**Rejection of Claims 1-10, 15-17**
**Under 35 U.S.C. §112(2¶)**

The Examiner considers: (a) recitation of "lipopolysaccharide endotoxin mediated pathology" in claims 1 and 6 to be vague and indefinite; (b) use of "lipopolysaccharide" to modify endotoxin in claims 1, 4, 5, 9, and 15 to be indefinite; and (c) "Rc chemotype" to be redundant when used with J5 in claims 2, 7 and 16. Applicants traverse all rejections.

(a) Applicants expressly define pathological conditions induced by the lipopolysaccharide endotoxin of Gram-negative bacteria (see specification at p. 3, line 15 *et seq.*; p. 3, lines 24-25; p. 4, lines 32-33; and p.5, lines 3-4). The specific symptoms that constitute LPS endotoxin-mediated pathology are well known to those skilled in this art. An appended excerpt from a standard textbook (Bellanti, IMMUNOLOGY III, W.B. Saunders, 1985, p. 267, EXHIBIT 1) lists such pathology as including shock, fever, leukopenia, hyperglycemis, intravascular coagulation and septicemia. Because this definition is common knowledge, applicants submit that it is not necessary to define "pathology" in relation to bacterial "LPS endotoxin-mediated pathology."

(b) Claims 4, 5, 9 and 15 have been amended as suggested by the examiner.

(c) *E. coli* J5 is a specific type of "Rc chemotype" and is not a redundancy. The description "*E. coli* J5 (Rc chemotype)" is designed to distinguish the present composition from others, e.g., *Salmonella minnesota* E5, which are also types of Rc chemotype. This distinction is generally recognized as such in the art (see *e.g.*, specification at p. 8 lines 3-4, and p.5 lines 5-8). The Examiner is respectfully requested to withdraw these rejections.

**Rejection Of Claims 1-10 and 15-17**
**Under 35 U.S.C. §112(1st ¶)**

The examiner alleges that: (a) it is not clear whether a rabbit is an art-recognized animal model of Group B meningococcal disease that is predictive of similar activity in humans; and (b) it is not clear whether the neutropenic rat is an art-accepted model for the generic Gram-negative bacteria and endotoxin mediated pathology that could reasonably be extrapolated dated to humans. To buttress her arguments, however, the Examiner cites older references that do not reflect the state of the current art.

As a threshold matter, applicants submit that this rejection is a "lack of utility" rejection thinly disguised as a rejection on nonenablement grounds. At the outset, the rejection is impermissible as it is in contravention of current M.P.E.P utility guidelines and recent Federal Circuit rulings. In citing *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) with approval, the Court in *In re Brana*, 51, F.3d 1560, 34 USPQ 3d 1436 (Fed. Cir. 1995) stated:

> From this (Marzocchi) it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.

Here, the examiner has not demonstrated that one skilled in this art would find incredible the predictive value of applicants' neutropenic rat model.

In referring to the references cited by the PTO to question the utility of compounds asserted to have anti-tumour activity, the *Brana* court stated:

> Rather, these references merely discuss the therapeutive predictive value of the *in vivo* murine tests-relevant only if the applicants must prove the ultimate value of their asserted utility in humans.

*Id.* Here, too, the examiner has pointed to no passage in any reference that disputes the claims of applicants as to the neutrogenic rat model.

Referring now to the specific points made by the examiner:

(a) The examiner appears to misunderstand the invention. Rabbits are not used as a test animal for the determination of the unmanotherapeutic efficacy of the inventive purified, detoxified LPS-OMP complex. Rather, the rabbit is used merely to determine the immunogenicity of the J5 LPS-GBOMP non-covalent complex vaccine (p.6, lines 16-17 and Example 7) and to for pyrogenicity of the aforementioned complex vaccine (Example 5). It is critical to understand that neither of these uses of the rabbit involves testing the efficacy of the complex vaccines of the invention (that is, immunotherapy against Gram-negative bacteria or against LPS endotoxin-mediated pathology. This immunotherapeutic use of the inventive vaccine is amply described in the specification. See, specification at, e.g., p. 3, lines 15, 17 and 23; p.4, lines 4, 12 and 31-32.

(b) As a threshold matter, the examiner is reminded that there is no requirement for an animal model

to develop a vaccine. Vaccines have been developed against poliomyelitis, meningoccus infection, pertussis and hepatitis B infection without the existence of an animal model. To date, there still are no animal models of these human diseases.

The neutropenic rat is generally accepted as an animal model for determining the efficacy of vaccines for immunotherapy against Gram-negative bacteria and endotoxin-mediated pathology. For example, see, Opal et al., 36th ICAAC, New Orleans, 1996, Abs., EXHIBIT 2; draft Consensus Report on FUTURE OF SEPSIS RESEARCH (ACCP, NIAID, NHLRI, 1996) at p. 10, last ¶; and at p. 11, first ¶, EXHIBIT 3; Cross *et al.*, Choice of Bacteria in Animal Models of Sepsis, a Minireview, *Infect. Immun.*, 61: 2741 (1993), EXHIBIT 4, copies of all of which are enclosed.

Further, in yet another system (efficacy of anti-endotoxin monoclonal antibody against *Pseudomonas* sepsis), another research group also used the neutropenic rat as an animal model of human sepsis. Romulo *et al.*, *J. Infect. Dis.*, 167: 126 (1993), EXHIBIT 5 (copy enclosed). In connection with this reference, it should also be noted that the Xoma Corp., Berkeley, CA has contracted with the Romulo *et al.* to use applicants' neutropenic rat model to test a murine-derived IgM mAb directed against a lipid A component of bacterial endotoxin E3, indicating the commercial importance of the present rat model (see p. 126, right column, first full paragraph)

Clearly, the art has progressed greatly since the days recalled by the Examiner in her citations of references, and rat models, in the absence of human research animals, are accepted in this art.

It also is established that "a rigorous correlation between animal test data and human therapeutic utility is not necessary if there is a satisfactory

correlation between the effect on the animal and that ultimately observed in humans. Evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to consider that the asserted utility is more likely than not true." M.P.E.P. §2107.01(f). Further, "applicants need not provide actual evidence of success in treating humans where such utility is asserted." M.P.E.P. §2107.02(a). "Data from *in vitro* or animal testing is generally sufficient to support therapeutic utility and operability." M.P.E.P. §2107.02(c) and (d). Further, the fact that there is no known cure for a disease cannot serve as the basis for a consideration that such an invention lacks utility. Rather, the Office must determine if the asserted utility for the invention is credible based on the description of the invention. M.P.E.P. §2107.02(f); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Unless the Office demonstrates a lack of utility of the invention, it cannot then reject the same claims under the enablement/operability statute. *Id*. The examiner has not demonstrated a lack of utility of the present invention.

The Examiner also asserts that applicants do not enable the *E. coli* LPS-GBOMP complex, as it does not teach how to use the complex as a vaccine. Applicants traverse this rejection.

The Examiner's attention is respectfully directed to page 22 of the specification where use is taught of the *E. coli* LPS-GBOMP complex vaccine antiserum to protect the neutropenic rat model of sepsis against *P. aeruginosa* (lines 4-31).

In addition, IgG, isolated from the post-immune serum of a rabbit previously immunized with J5 LPS-NM GBOMP non-covalent complex vaccine, is shown to protect the rat model against challenge with lethal doses of a

virulent strain of *P. aeruginosa* attack (lines 32-37, p. 23, lines 1-2.

Further, in control experiments, IgG, prepared from pre-immune serum of a rabbit previously immunized with the J5 DLPS-NMGBOMP complex vaccine, failed to protect the rat models (lines 3-8).

As noted above, the immunogenicity of J5 LPS-NM vaccines and J5 DLPS-NMGBOMP vaccines were tested in rabbits (Examples 7 and 8) at prescribed dosages.

Finally, methods of using such vaccines are taught in the art. See, Opal and Drabick et al., 36th ICAAC, New Orleans, LA, Abstract enclosed, Exhibit 6.

Those skilled in the art of vaccines will know how to project from animal dosages to a regimen for humans, if necessary.

The Examiner is respectfully requested to withdraw these rejections as well.

**Rejection Under 35 U.S.C. §102(b)**

Claim 1 is rejected as allegedly anticipated by Zollinger U.S. Patent 4,707,545 which is said to disclose in column 1 complexes comprised of LPS and purified OMP from *N. meningitides*. Applicants traverse this rejection.

As the examiner knows well, a reference may defeat novelty only if all recitations in the claim under review are be present within the four corners of that reference. Amended claim 1 requires that the LPS endotoxin derived from *E. coli* be purified and detoxified and that the OMP from *N. meningitides* be purified. The combination of purified and detoxified LPS endotoxin and purified OMP is not disclosed in column 1 of Zollinger. Hence, this reference cannot be said to anticipate present claim 1,

and the Examiner is respectfully requested to withdraw this rejection.

**Rejection Under 35 U.S.C. §103**

Claims 1-10 and 15-17 are rejected as obvious over Zollinger *et al.*, U.S. Patent 4,707,543. This reference is said to teach the use of detoxified LPS-OMP complexes as vaccines to protect animals against infection. The detoxified LPS is said to be derived from *E. coli* and OMP from *N. meningitides*. The Examiner speculates that similar results may be attained using any complex comprising a detoxified LPS and *N. meningitides* OMP. Applicants traverse these rejections.

With respect, the Examiner appears not to have appreciated the distinctions between the Zollinger patent and the present invention. The basic distinction between the two, which applicants will elaborate upon below, is that Zollinger is directed primarily to the process for preparing polysaccharide-OMP complexes and secondarily to testing the bacteriocidal activity of the complex (column 14, lines 37 *et seq.*), whereas the present invention (in which Zollinger is a co-inventor) is directed to the immunoregulatory properties of a complex comprising a purified, detoxified J5 LPS (DLPS) from *E. coli* and purified OMP from *N. meningitides*, said properties consisting of active or passive immunization of a subject against Gram-negative bacteria and LPS-mediated pathology (p. 4, lines 27 *et seq.*). Only the present J5 LPS endotoxin works in this respect.

Zollinger proposed that an OMP-LPS vaccine would generate type-specific antibodies against meningococci that would be bactericidal for that one serotype. They also proposed that complexing the LPS from other gram-

negative bacteria may similarly induce the formation of antibodies that mediate either the direct killing of the viable type-specific bacteria or indirectly mediate that killing through the induction of type-specific opsonic antibody. Thus, the properties suggested for the complex in Zollinger are characterized by (1) the induction of type-specific antibody that can (2) enhance the killing of type-specific bacteria and ultimately to (3) prevent infection.

The J5 subunit vaccine in the present invention is therefore entirely different and is not suggested by Zollinger. A key aspect of applicants' vaccine is reflected in their demonstration that the LPS from an LPS of *E. coli* J5 (Rc chemotype) can produce antibodies that provide protection against the biologic activities of heterologous LPS, and do not kill bacteria. Thus, antibodies directed against a common epitope in a highly conserved region of LPS interrupts multiple inflammatory mediator cascades initiated by a non-viable portion of the gram-negative bacteria. These antibodies do not prevent infection [Opal *et al.*, above] and applicants' complex does not promote the killing of bacteria, either directly or indirectly. Accordingly, the insights underlying the J5 subunit vaccine are entirely different from, and not presaged by, the teachings of, Zollinger. The only similarities to the Zollinger description is the use of the OMP as an adjuvant. The uniqueness of the present vaccine does not lie in the particular adjuvant used; other adjuvants or forms of presentation of the J5 LPS may also elicit anti-endotoxin antibodies.

The importance of the present J5 LPS component in differentiating the claimed invention from the Zollinger patent is that applicants' vaccine has properties completely unrelated to the infectious disease application

described by the Zollinger patent. Most importantly, there is now a body of literature suggesting that anti-endotoxin antibodies similar to those elicited by this vaccine may also have a role in the treatment of graft-versus-host disease in transplantation patients. The observation that patients who had high levels of anti-endotoxin antibodies had a decreased incidence of graft-versus-host disease has led investigators to hypothesize that endotoxin leaking into the circulation may act as an immune stimulant that initiates this important complication in patients who have received bone marrow transplantation. No interpretation of the Zollinger teachings have suggested this situation.

In another emerging area, there are numerous observations that the presence of anti-endotoxin antibodies may ameliorate the manifestations and course of heat stroke. These prospects for the use of the J5 subunit illustrate the unique nature of applicants' vaccine that differentiates it from the Zollinger disclosure.

In their landmark study, Ziegler *et al.* (of record) demonstrated that a vaccine made from J5 *E. coli* could induce an antiserum that prevented mortality from septic shock. In that study, however, they were unable to identify antibodies as a basis for that protection. Moreover, while it was assumed that the LPS portion of the J5 boiled bacteria was the active immunogen, that hypothesis was never substantiated before applicants' discoveries. Since that 1982 study, others have attempted to induce protective antibodies from the J5 *E. coli*. All have been unsuccessful and none have focused on the purified LPS as a potential vaccine candidate. A distinctive insight underlying applicants' vaccine, therefore, is the recognition that a purified and detoxified portion of the J5 bacterium could induce the

protective elements independent of the whole bacterium and could be presented in a manner that was acceptable for human use (*i.e.*, detoxification of the otherwise poorly tolerated LPS).

Another aspect of the present invention is evident in the demonstration that this purified and detoxified J5 LPS induces antibodies that can mediate protection independently of whole serum, and that the IgG isotype that predominates in commercially available gammaglobulin preparations can provide this protection. In the nearly fifteen years since the publication of the first J5 clinical study, no investigator has been able to demonstrate a role for J5 antibodies in general and IgG in particular. Calandra *et al.* 1988, of record. Applicants are the first.

Applicants' invention is not founded solely on an animal model. The animal model has, however, allowed applicants and others to demonstrate efficacy of this vaccine in a process initiated by a heterologous bacteria, *Pseudomonas aeruginosa*, and to show that, while it might reduce the induction of inflammatory mediators following endotoxemia, the anti-endotoxin antibodies do not reduce circulating bacteria as would be predicted from the vaccine constructs proposed by Zollinger. The use of this animal model has also permitted the demonstration that this vaccine could induce protection when given actively. Opal, *op cit*.

For these many and sufficient reasons, the examiner is respectfully requested to withdraw all rejections under §103.

In summary, applicants submit that it is the unique and unobvious nature of the purified, detoxified J5 LPS component of the present vaccine complex that merits a separate patent.

All claims are now in a form suitable for allowance, and early notification of allowance is respectfully requested. The Examiner is invited to call the undersigned at (202) 672-5554 if there are points that can be cleared up by an examiner's amendment.

Respectfully submitted,

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